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Rössler, W ; Hengartner, M P ; Angst, J ; Ajdacic-Gross, V

Abstract: Aims The aim of the study was to examine the temporal associations between substance use and subclinical psychosis symptoms. Design Data from a prospective community study sampled within a single cohort over 30 years (1978–2008) were analysed with discrete-time hazard models. Setting General population-based sample. Participants At initial sampling in 1978 males (n = 292) were 19 and females (n = 299) were 20 years old. Measurements Two psychosis syndromes representing 'schizotypal signs' and 'schizophrenia nuclear symptoms' and various substance use variables including cannabis, alcohol, tobacco and multiple-drug use (i.e. cannabis combined with other drugs). Findings In bivariate analyses, schizotypal signs were predominantly associated with regular cannabis use in adolescence (OR = 2.29, 95% CI 1.32–3.97). Schizophrenia nuclear symptoms were mainly related to alcohol (OR = 1.84, 95% CI 1.00–3.38) and multiple-drug use (OR = 2.35, 95% CI 1.38–4.02) during adolescence. Multivariate analyses showed that, in particular, regular cannabis use during adolescence was associated with the occurrence of subsequent schizotypal symptoms over a 30-year period (OR = 2.60, 95% CI; 1.59–4.23), whereas multiple-drug use in adolescence was associated predominantly with schizophrenia nuclear symptoms (OR = 1.75, 95% CI 1.01–3.03). Alcohol misuse was only slightly associated with the onset of such symptoms. Conclusions A significant portion of the occurrence of subclinical psychosis symptoms in adulthood can be attributed to excessive cannabis and multiple-drug use during adolescence. This is in line with the hypothesis that long-term sensitization of dopaminergic brain receptors plays a role in developing psychotic symptoms.

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Linking substance use with symptoms of sub-clinical psychosis in a community cohort over 30 years

Wulf Rössler[1,2], Michael P. Hengartner[1], Jules Angst[1] & Vladeta Ajdacic-Gross[1]

[1] Psychiatric University Hospital Zurich, Department of General and Social Psychiatry, Zurich, Switzerland

[2] Collegium Helveticum, a Joint Research Institute between the University of Zurich and the Swiss Federal Institute of Technology, Zurich, Switzerland

Address for correspondence;

Wulf Rössler, MD, MSc

Department of General and Social Psychiatry

Psychiatric University Hospital, University of Zurich

Militärstrasse 8

CH-8004 Zurich

Tel.: (+41) 44 2967400

Fax: (+41) 296 7409

Email: roessler@dgsp.uzh.ch

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Abstract

Aims: The aim of the study was to examine the temporal associations between substance use and sub-clinical psychosis symptoms. **Design:** Data from a prospective community study sampled within a single cohort over 30 years (1978-2008) were analyzed with discrete-time hazard models. **Setting:** General population based sample. **Participants:** At initial sampling in 1978 males (N=292) were 19 and females (N=299) were 20 years old. **Measurements:** Two psychosis syndromes representing “schizotypal signs” and “schizophrenia nuclear symptoms” and various substance use variables including cannabis, alcohol, tobacco and multiple-drug use (i.e. cannabis combined with other drugs). **Findings:** In bivariate analyses, alcohol (OR=1.48, 95%-CI=1.05-2.09), tobacco (OR=1.76, 95%-CI=1.09-2.82), and cannabis (OR=2.29, 95%-CI=1.32-3.97) were associated with schizotypal signs. Schizophrenia nuclear symptoms were related to alcohol (OR=1.84, 95%-CI=1.00-3.38), cannabis (OR=1.59, 95%-CI=1.03-2.46), and multiple-drug use (OR=2.35, 95%-CI=1.38-4.02). Multivariate analyses showed that in particular regular cannabis use during adolescence was associated with the occurrence of subsequent schizotypal symptoms over a 30-year period (OR=2.60, 95%-CI=1.59-4.23), whereas multiple-drug use in adolescence was predominantly associated with schizophrenia nuclear symptoms (OR=1.75, 95%-CI=1.01-3.03). Alcohol misuse was only slightly associated with the onset of such symptoms. **Conclusions:** A significant portion of the occurrence of subclinical psychosis symptoms in adulthood can be attributed to excessive cannabis and multiple-drug use during adolescence. This is in line with the hypothesis that long-term sensitization of dopaminergic brain receptors plays a role in developing psychotic symptoms.

Keywords: substance abuse, cannabis, alcohol, sub-clinical psychosis, psychotic experiences, schizophrenia, epidemiology

Introduction

Dopamine disregulation is a central component in the pathogenesis of schizophrenia [1-3]. Heightened dopaminergic neurotransmission likely leads to an aberrant assignment of salience to normal stimuli as a precursor of full blown psychosis [4]. The capacity to increase dopamine levels in the central nervous system also is a common feature of all substances with addictive potential, including cocaine, amphetamine, alcohol, opioids, nicotine, and cannabis [5]. The use of these substances, alone or in combination, is widespread among adolescents and can provoke psychotic symptoms [6]. Notably several studies have found a positive association between cannabis use and psychosis [7-11]. For reviews see [12,13]. To our knowledge, however, no research within a prospective, longitudinal community sample has focused on temporal associations between different patterns of substance use and the subsequent occurrence of sub-clinical psychosis symptoms. Therefore, our objective was to examine the age-related effects of multiple substance use as they apply to the development of sub-clinical symptoms over a 30-year period.

Method

Sample

The sampling method for the Zurich Study was based on a two-phase procedure described by Dunn et al [14]. Fairly common in epidemiological research, it is characterized by both screening and interviews. The latter is carried out with a subsample of initially screened subjects, and is typically stratified along selected criteria and cut-offs. In statistical analysis, those stratified data must be weighted to receive correct point estimates, such as prevalence rates.

In 1978, we sampled 4547 subjects (2201 males, 19 years old; 2346 females, 20 years old) who were considered representative of the canton of Zurich in Switzerland. Male and female participants were sampled with different approaches. In Switzerland every male person has

to undertake a military screening test at the age of 19. Therefore conscripts of a defined catchment area represent the respective complete male age group. With the consent of the military authorities but independent of their screening procedure, we randomly screened 50% of all male conscripts of this age group. The refusal rate was 0.3%. The female participants of the age 20 were identified from the complete electoral register. Again, 50% of these women were randomly selected and received questionnaires by mail; 75% of them responded. All 4547 subjects received a demographic questionnaire and the Symptom-Checklist 90-Revised (SCL-90-R) [15]. The SCL-90-R is a comprehensive self-report questionnaire of 90 items, which cover a broad range of psychiatric symptoms. Because a lower educational level was over-represented among the non-responding women, we corrected that by matching the educational levels between females and males during the screening process.

For the second sampling phase, we applied a stratification procedure to enrich the interview sample with cases at risk for the development of psychiatric syndromes. Stratification was based on a cut-off value of the SCL-90-R global severity index (GSI) score, which was obtained in the initial screening-phase as specified above. That means that two-thirds of the final interview sample comprised randomly drawn high scorers (defined by the 85th percentile or above on SCL-90-R GSI scores) from the screening-sample of 4547 subjects while the remaining third were randomly selected from the rest of the screening-sample (GSI scores below the 85th percentile). The GSI cut-off values were 1.57 and 1.89 for males and females, respectively. In all 591 subjects (292 males, 299 females) were chosen with this procedure.

Face-to-face interviews were conducted in 1979 (participants aged 20/21), 1981 (22/23), 1986 (27/28), 1988 (29/30), 1993 (34/35), 1999 (40/41), and 2008 (49/50). The numbers of participants are indicated in Figure 1. The different assessments waves were conducted within 1 to 1.5 years. Over the entire time span of 30 years, 57% of the original interview-sample continued to participate. Those who dropped out did not differ significantly in their demographics from those subjects who remained in the study. The initial allocation to the two

groups split through the cut-off of the 85th percentile of the GSI has not changed over the time span, although drop-outs were rather extremely high or low scorers on the GSI [16].

(Insert Figure 1 here)

Instruments

Interviews were conducted according to the "Structured Psychopathological Interview and Rating of the Social Consequences of Psychological Disturbances for Epidemiology" (SPIKE) [17]. This semi-structured interview, developed for epidemiological surveys in psychiatric research, assesses data about socio-demography, psychopathology, substance use, medication, health services use, impairment, and social activity. Its reliability and validity have been reported previously [18]. Clinical diagnoses of psychotic disorders could not be assessed with the SPIKE because the required criteria were not included in the interviews from 1979 up to 1999. For the interview from 2008 an additional chapter on psychosis was included in the SPIKE. This section allowed us to provide a 12-month diagnosis of broad psychosis, which is based on DSM-IV criteria for schizophrenia. According to that algorithm no participant fulfilled the criteria for a DSM-IV psychosis.

In addition to the information from the SPIKE, we also used the SCL-90-R during all assessment waves, in which subjects responded according to a five-point Likert scale of distress that ranged from "not at all" (1) to "a little bit" (2), "moderately" (3), "quite a bit" (4), and "extremely" (5). The SCL-90-R covered the most recent four-week period psychopathology for each time of measurement. Its 90 items are grouped along nine subscales that reflect a broad spectrum of symptoms. We applied two SCL-90-R subscales relevant to psychosis ("paranoid ideation" and "psychoticism"). According to the SCL-90-R manual, six items within the former subscale, as originally designed, characterize projective thoughts, hostility, suspicion, grandiosity, centrality, fear of losing autonomy, and delusions. The latter subscale (10 items) includes terms indicative of a socially withdrawn, isolated,

schizoid lifestyle, as well as those that represent symptoms of psychosis and schizophrenia, e.g., hallucinations and thought-broadcasting.

Measures

The SCL-90-R has historically shown good internal consistency and test–retest reliability [19,20]. However, the factor structure of that instrument has led to contradictory results. Commonly, fewer than nine factors are identified [20], and the "psychoticism" subscale yields the least consistent data [21]. Such discrepancies have been reported since the very first stages of developing this questionnaire [15].

Because of these inconsistencies, we used factor analysis with the PROC FACTOR procedure of SAS (V8.2/Windows) and Promax rotation to challenge those "paranoid ideation" and "psychoticism" subscales. Our repeated waves of assessment over 30 years allowed us to replicate and, thus, validate the factor structure. All analyses were confined to those two subscales. Items that consistently loaded jointly on the same factor over six waves were then selected for building two new subscales. These steps led to a slight rearrangement of respective items from the original subscales (Table 1). Our first new subscale matched the original paranoid ideation subscale but added the items "feeling lonely even when with people", and "never feeling close to another person" from the original "psychoticism" subscale. This subscale was used to address social and interpersonal deficiencies with reduced capacity for close relationships as well as ideas of reference, odd beliefs, and suspicion/paranoid ideation. As such, this factor was reminiscent of criteria required for diagnosing a "schizotypal personality disorder". Thus we named this new subscale "schizotypal signs".

Our second new subscale included the items of thought insertion, thought-broadcasting, thought control, and hearing voices, all from the original "psychoticism" subscale. These represent attenuated forms of the nuclear symptoms of schizophrenia. We named this the "schizophrenia nuclear symptoms" subscale. For that, three items on the original

“psychoticism” subscale were eliminated while two others were shifted to the new “schizotypal signs” subscale. We have previously detailed the construction of those two psychosis dimensions [22]. Our rearranged subscales have now been applied in various other studies [23-25] and have also been confirmed recently through a principal component analysis for a population of about 5000 participants in the Netherlands [26]. Hence, we conclude that our revised and independently verified SCL-90-R subscale structure presents psychosis symptoms in that questionnaire in a more adequate and stable manner.

(Insert Table 1 here)

Because some statistical procedures required dichotomous variables (see below), we defined the occurrence of psychotic symptoms as scoring at least as high as the 85th percentile on each psychosis subscale. Single or occasional psychotic symptoms that arise without functional impairment are quite prevalent in the general population, with prevalence rates between 10% and 15% [22,27]. Therefore, we chose that cut-off to include preferably pronounced but sub-threshold symptoms in our analysis. The dichotomous psychotic symptom variables assessed retrospectively the four-week prevalence rate of those symptoms at all interview waves, i.e. in 1979, 1981, 1986, 1988, 1993, 1999, and 2008. Participants were classified as adolescents up to 19/20 years old and as adults from 19/20 to 49/50. Substance use was grouped according to the recorded information concerning substance use during adolescence versus adulthood. The exception was for multiple-drug use, which was only evaluated for the category of youngest participants. Because the screening was conducted at age 19/20 (in the year 1978), the assessment of substance use up to that age was necessarily retrospective. The following interviews always encompassed the last twelve months prior to the respective interview. To assess substance use up to the age 19/20, participants were asked to indicate how frequently they used a given substance if ever used up to that age. In all subsequent interviews participants were asked if they had

used a given substance during the previous twelve months. All information about substance use was assessed with the SPIKE. The variables considered for substance use included:

- For cannabis: no use; casual (up to three times per month); or regular (once per week up to daily).
- For frequency of alcohol intoxication in adolescence: no intoxication; casual (having 1 to 10 intoxications until age 19/20); or regular (having 11 and more intoxications until age 19/20).
- For alcohol misuse in adulthood: yes vs. no (according to DSM-III, III-R, and IV criteria for alcohol abuse and/or dependence).
- For frequency of alcohol use in adulthood: once per week or less vs. several times per week.
- For onset of tobacco use: adolescence (up to the age of 19/20) vs. adulthood (after age 19/20).
- For magnitude of tobacco use: less than 20 cigarettes and none vs. 20 cigarettes and more.
- For multiple-drug use during adolescence: yes vs. no (multiple-drug use comprises cannabis and at least one other substance, e.g., LSD, mescaline, speed, or other amphetamines).

For adjustment of the associations between substance use and psychotic symptoms we used the following covariates: sex, familial background (raised by no biological parent, one parent, or both parents; or adopted), socio-economic status (i.e., parents' income), family history of mental disorders, other family problems (i.e., harsh punishments, neglect, or conflicts with parents), and school problems (i.e., conflicts with teachers and peers, bullying, or performance pressure). All covariates were assessed with the SPIKE. Family and school problems were assessed in the interviews from 1986 and 1988, respectively. All other variables were provided in the first interview in 1979.

Statistical analyses

Post-hoc power analyses were carried out with G*Power 3 [28] using a two-tailed test and α=0.05. Power was estimated for samples sizes N=591 and N=335, respectively. Associations between substance use and psychotic symptoms were evaluated with discrete-time hazard models, i.e., via survival analyses. Information was arranged into a *longitudinal person–period data set,* in which an individual had multiple records for every repeated measure. The total number of records in the response categories of a given substance use variable is indicated in Tables 2-5. Each entry for an individual was configured as a new record, defining each event occurrence as a dichotomous variable for every year of the data assessment (i.e., a target event occurred or did not occur at follow-up). The recording of further events stopped after a subject had experienced the target event, which was defined as having happened when a subject first scored at least as high as the 85th percentile on our newly defined psychosis subscales. This we also referred to as the occurrence of "schizotypal signs" or "schizophrenia nuclear symptoms". For example, if a subject first reported such defined symptoms higher or equal the 85th percentile at the third interview wave, three data entries in every psychosis subscale were recorded for him or her, i.e. one for each completed interview (i.e., 1979, 1981, and 1986). Censoring occurred when a subject either definitively dropped out of the cohort or never experienced the target event after all follow-ups.

Discrete-time hazard models rely on binary logistic regressions with longitudinal data. Their statistical framework has been described by Singer and Willett [29]. Initially, we conducted series of bivariate analyses of substance use and psychotic symptoms for separate substance-use variables. Each was adjusted for sex, familial background, socio-economic status, family history of mental disorders, other family problems, and school problems. In contrast, for multivariate analyses, all variables were entered simultaneously, using a forward step-wise (likelihood ratio) method. In the multivariate models we included all such variables that had shown significant associations in our bivariate analyses. The models adjusted each

variable for all others. To avoid biased results through multi-collinearity we excluded predictor variables that were intercorrelated greater than 0.5. Intercorrelation of the predictor variables was analyzed with Spearman coefficients.

All statistical analyses were conducted with SPSS version 17 for Macintosh.

Results

Power analyses

Post-hoc power analyses revealed that for a binomial predictor variable with an OR=2.0 the statistical power (1-β error probability) was reduced from 0.92 for N=591 to 0.69 for N=335. For an OR=1.8 the power was reduced from 0.80 for N=591 to 0.54 for N=335. Those two odds ratio estimates correspond to a moderate effect size.

Bivariate analyses

The bivariate analyses showed that scores ranking equal to or higher than the 85th percentile on the “schizotypal signs” subscale were significantly associated with the use of cannabis, alcohol, and tobacco (Table 2). Altogether, 5 out of 8 substance-use variables were significantly associated with high scores on the “schizotypal signs” subscale over the 30 years assessed. The strongest associations were found for casual (OR=1.80, 95%-CI=1.22-2.66, p=0.003) and regular (OR=2.29, 95%-CI=1.32-3.97, p=0.003) cannabis use in adolescence. The cumulative survival rate over time for cannabis use in adolescence is shown in Figure 2. The graph illustrates the occurrence of schizotypal signs over time in association with early cannabis use and demonstrates a clear dose-response relationship.

(Insert Figure 2 here)

(Insert Table 2 here)

The bivariate associations for the subscale of “schizophrenia nuclear symptoms” were slightly weaker than those for the first subscale (Table 3), with only 3 of 8 substance-use variables being significantly associated with the occurrence of such symptoms. Furthermore, tobacco use was not significantly correlated. The strongest associations were found for regular alcohol intoxication in adolescence (OR=1.84, 95%-CI=1.00-3.38, p=0.049) and for multiple-drug use in adolescence (OR=2.35, 95%-CI=1.38-4.02, p=0.002). The cumulative survival rate over time for multiple-drug use in adolescence is shown in Figure 3. Further figures for the other substance-use variables can be provided on request.

(Insert Figure 3 here)

(Insert Table 3 here)

Multivariate analyses

The correlation matrix showed that there were no intercorrelations greater than 0.5 between the bivariate predictors of the “schizotypal signs” and therefore all variables were included in a multivariate model. The multivariate model of the “schizotypal signs” yielded two significant predictors for high scores on the “schizotypal signs” subscale (Table 4) – the frequency of cannabis use in adolescence (for casual use: OR=1.80, 95%-CI=1.24-2.59, p=0.002; for regular use: OR=2.60, 95%-CI=1.59-4.23, p<0.001) and alcohol misuse in adulthood (OR=1.39, 95%-CI=1.02-1.90, p=0.040).

Intercorrelations of the bivariate predictors of the “schizophrenia nuclear symptoms” were also smaller than 0.5 and therefore all variables were included in the multivariate model. The multivariate analyses of the “schizophrenia nuclear symptoms” subscale (Table 5) revealed that the frequency of alcohol intoxication in adolescence (for casual intoxication: OR=1.59, 95%-CI=1.14-2.21, p=0.006; for regular intoxication: OR=1.69, 95%-CI=0.91-3.14, p=0.099)

and multiple-drug use in adolescence (OR=1.75, 95%-CI=1.01-3.03, p=0.047) were significantly predictive of high scores on the respective psychosis scale.

(Insert Table 4 here)

(Insert Table 5 here)

Discussion

To our knowledge this is the first study linking substance use and sub-clinical psychotic symptoms over 30 years and within a community cohort. For most substances, those associations presented here were moderately but persistently positive with psychotic symptoms. In the bivariate analyses, all substance-use variables were adjusted for numerous parameters, including familial background, socio-economic status, family history of mental disorders and other problems, as well as conflicts met in school. Because our records on substance use were so detailed, we could adjust each pattern of use toward other substances in the multivariate analyses. This enabled us to evaluate the impact of different substances independently and in relation to their frequency of use as reported by the participants of the study.

The psychosis symptoms studied here do not reach the threshold for a diagnosis of schizophrenia. However, considering the dimensional character of psychosis, it seems quite important that the occurrence of psychotic symptoms should be assessed below such a threshold, particularly with regard to preventive measures.

The common denominator for all substances analyzed in this project is their potential impact on dopamine transmission or release. As such they can contribute to the occurrence of psychosis symptoms where dopaminergic disregulation plays an important role [1,2]. The temporal gap between the assessment of substance use in adolescence and symptoms

manifested during adulthood makes it unlikely that those substances have only an immediate or acute impact. Rather, the respective brain receptors are sensitized for a psychotic response in the long term [30,31].

But we are aware that other factors might contribute as well. We ourselves found in a previous study [22], that cannabis use in adolescence was associated specifically with schizophrenia nuclear symptoms, whereas childhood adversity as well as chronic physical or mental disorders in parents contributed to schizotypal signs. Individuals with a persistently high level of either of the two identified symptom dimensions over 20 years experienced significant deficiencies in social achievement and functioning. Therefore we deliberately adjusted for a broad range of covariates in the present study.

Our bivariate analyses are in accord with those reported elsewhere. For example, in healthy subjects, cannabis use and alcohol abuse are associated with the incidence of psychotic experiences [32-35]. Alcohol abuse also can induce psychotic disorders [36]. Moreover, empirical evidence has demonstrated that alcohol use is correlated with subsequent brain abnormalities and increased risk of psychosis in subjects at high genetic risk for schizophrenia [37]. Regular tobacco use has also been found to relate to the occurrence of psychotic symptoms [9,32] with the onset of the former preceding that of the latter [38,39]. Multiple-drug use has not yet been shown to have any additional long-term influence on the occurrence of psychotic symptoms or schizophrenia. In bivariate analyses that followed the subscale of “schizophrenia nuclear symptoms”, we found considerably higher OR values for multiple-drug use (i.e., cannabis plus at least one other drug) compared with the use of cannabis alone ore no cannabis use during adolescence. In the multivariate analysis, when adjusting for other substances, multiple-drug use was still significantly related to “schizophrenia nuclear symptoms”. Substances such as LSD, mescaline, and speed can immediately cause psychosis-like symptoms [6]. Furthermore, they appear to have delayed effects on the occurrence of symptoms when cannabis is the primary factor, whereas cannabis use alone did not yield the same effect [31]. A recent review [40] of associations

between stimulants (speed or cocaine) and psychosis supports this finding. A plausible explanation for this could be that cannabis and other drugs interact in the dopaminergic system and consequently worsen the outcome.

Finally, we also provide further evidence for the existence of a dose-response relationship, in that greater cannabis use during adolescence and adulthood leads to higher OR values for psychosis symptoms. Prospective studies of the associations between cannabis use and later psychosis in the general population have determined that the risk of psychotic outcomes is enhanced in individuals who use cannabis very frequently [7,12].

Strengths and limitations

We believe that our prospective evaluation is the first to examine not only several substances but also their patterns of use as they relate to the development of sub-clinical psychotic syndromes. Although its longitudinal design means that our results can contribute to aetiological research, our analyses do not allow us to make definitive causal conclusions. For many of the significant associations identified here, a causal link seems to be quite plausible. This is especially true for cases where substance use assessed during adolescence preceded the occurrence of psychosis symptoms in adulthood. In our analyses this pertained to cannabis, alcohol, or multiple drugs. Furthermore, our results seem to be quite robust as we could control for several potential confounders. By focusing on sub-threshold syndromes, we have presented evidence for an association that is quite common in the general population and which does not restrict the validity of the results only to specific or rare, high-risk populations. Population-based studies allow researchers to investigate the association between substance use and incident psychotic symptoms before psychopathology becomes clinically relevant.

Despite the strengths described here, this study also has some limitations. First, the sample size was initially small and was then further reduced by attrition. This markedly diminished our statistical power for predictor categories that comprised relatively few qualifying

participants (e.g., those who reported regular cannabis use in adulthood). Second, we could not derive an exact temporal order because, at each time of measurement, we recorded only the 12-month prevalence for substance use and a 4-week prevalence for psychotic symptoms. Some intervals between interview waves also were quite long, making it impossible for us to determine whether participants had used substances or experienced psychotic symptoms during those gaps that were not covered by the interviews. We were similarly not able to assess psychotic symptoms prior to 1979, wherefore some participants may have shown the symptoms in question already before they started to use substances. Even if so, they still reported more psychotic symptoms after the onset of substance use. Furthermore, as indicated in Figures 2 and 3 psychotic symptoms rather occur many years after the beginning of substance use. Overlooking the 30 years time interval we can state that in may cases there is a clear temporal order, i.e. that in many cases the occurrence of psychotic symptoms is preceded by substance use. Third, the information assessed and analyzed here relied on self-report instruments for which responses might have been biased by omissions or intentional concealment. Nevertheless, because all of the data collected were held in strict confidence, we choose to assume that most reports were reliable. If we imply a major bias concerning the assessment of substance use, we would preferably expect an underreporting of substance use, which in turn would result in a decrease and underestimation of the association between substance use and psychotic symptoms.

In summary we believe that we could make a contribution to a more rational discussion in this field. Data from a prospective community study sampled within a single cohort over 30 years demonstrate that a significant portion of the occurrence of sub-clinical psychotic symptoms in adulthood can be attributed to excessive cannabis and multiple-drug use during adolescence. In this context it is very important to understand the early phases within a pathogenetic process when trying to prevent the onset of a certain illness. These would include alcohol and cannabis, in particular, because their use is amenable to preventive measures. Young people should be provided with information about the risks of substance

use even more as sub-clinical psychotic symptoms also put a strain on one's personal relationships and professional career [22].

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Table 1:

Items for new subscales of “schizophrenia nuclear symptoms” and “schizotypal signs” that replace those for the “paranoid ideation (PN) and “psychoticism” (PS) subscales from the original SCL-90-R.

New SCL-90-R items		Original SCL-90-R subscale[a]
“Schizophrenia nuclear symptoms” subscale		
7:	Someone else can control your thoughts	PS
16:	Hearing voices other people do not hear	PS
35:	Other being aware of your thoughts	PS
62:	Having thoughts that are not your own	PS
“Schizotypal signs” subscale		
8:	Others are to blame for your troubles	PN
18:	Feeling most people cannot be trusted	PN
43:	Feeling you are watched by others	PN
68:	Having ideas others do not share	PN
76:	Others not giving you proper credit	PN
77:	Feeling lonely even when with people	PS
83:	Feeling people take advantage of you	PN
88:	Never feeling close to another person	PS

[a] Items excluded from the original PS subscale are 84: Thoughts about sex that bother you a lot; 85: Idea you should be punished for sins; 87: Idea something is wrong with body; and 90: Idea something is wrong with your mind.

Table 2:

Discrete-time hazard models for bivariate associations between substance use and the occurrence of high scores on the "schizotypal signs" subscale. Values for significant associations are indicated in bold.

Substance-use variables[a]		**Occurrence of target event**	
		OR (95% CI)	N of target events (%)
Frequency of cannabis use in adolescence:	None (N=1749)	1 (Reference)	144 (8.2)
	Casual (N=320)	**1.80 (1.22-2.66)**	46 (14.4)
	Regular (N=131)	**2.29 (1.32-3.97)**	26 (19.8
Frequency of cannabis use in adulthood:	None (N=1838)	1 (Reference)	160 (8.7)
	Casual (N=257)	1.47 (0.94-2.29)	35 (13.6)
	Regular (N=128)	**1.80 (1.00-3.22)**	22 (17.2)
Frequency of alcohol intoxication in adolescence:	No intoxication (N=901)	1 (Reference)	65 (7.2)
	Casual (N=1130)	**1.48 (1.05-2.09)**	124 (11.0)
	Regular (N=163)	1.74 (0.96-3.16)	22 (13.5)
Alcohol misuse in adulthood:	No (N=2061)	1 (Reference)	197 (9.6)
	Yes (N=162)	1.66 (0.92-2.98)	20 (12.3)
Frequency of alcohol use in adulthood:	Once per week or less (N=1584)	1 (Reference)	140 (8.8)
	Several times per week (N=622)	**1.41 (1.01-1.99)**	75 (12.1)
Onset of tobacco use:	Never (N=748)	1 (Reference)	58 (7.8)
	Adolescence (N=1239)	1.38 (0.97-1.96)	136 (11.0)
	Adulthood (N=236)	1.05 (0.57-1.91)	23 (9.7)
Tobacco use in adulthood:	Less than 20 cig./none (N=2024)	1 (Reference)	189 (9.3)
	20 cigarettes or more (N=199)	**1.76 (1.09-2.82)**	28 (14.1)
Multiple-drug use in adolescence:	No multiple-drug use (N=1975)	1 (Reference)	174 (8.8)
	Multiple drugs (N=160)	1.59 (0.93-2.71)	25 (15.6)

[a] Adjusted for sex, familial background, socio-economic status, family history of mental disorder, and other problems with family or school. The N behind the response categories refers to the number of records.

Table 3:

Discrete-time hazard models for bivariate associations between substance use and the occurrence of high scores on the "schizophrenia nuclear symptoms" subscale. Values for significant associations are indicated in bold.

Substance-use variables[a]		**Occurrence of target event**	
		OR (95% CI)	N of target events (%)
Frequency of cannabis use in adolescence:	None (N=1641)	1 (Reference)	162 (9.9)
	Casual (N=340)	1.13 (0.74-1.73)	37 (10.9)
	Regular (N=126)	1.73 (0.96-3.11)	22 (17.5)
Frequency of cannabis use in adulthood:	None (N=1755)	1 (Reference)	168 (9.6)
	Casual (N=250)	**1.59 (1.03-2.46)**	36 (14.4)
	Regular (N=121)	1.77 (0.96-3.24)	19 (15.7)
Frequency of alcohol intoxication in adolescence:	No intoxication (N=853)	1 (Reference)	68 (8.0)
	Casual (N=1088)	**1.53 (1.08-2.17)**	128 (11.8)
	Regular (N=153)	**1.84 (1.00-3.38)**	22 (14.4)
Alcohol misuse in adulthood:	No (N=1955)	1 (Reference)	205 (10.5)
	Yes (N=171)	1.53 (0.82-2.85)	18 (10.5)
Frequency of alcohol use in adulthood:	Once per week or less (N=1522)	1 (Reference)	155 (10.2)
	Several times per week (N=590)	1.10 (0.78-1.56)	68 (11.5)
Onset of tobacco use:	Never (N=703)	1 (Reference)	63 (9.0)
	Adolescence (N=1216)	1.29 (0.74-2.24)	128 (10.5)
	Adulthood (N=207)	1.18 (0.83-1.69)	32 (15.5)
Tobacco use in adulthood:	Less than 20 cig./none (N=1917)	1 (Reference)	192 (10.0)
	20 cigarettes or more (N=209)	1.52 (0.95-2.41)	31 (14.8)
Multiple-drug use in adolescence:	No multiple-drug use (N=1876)	1 (Reference)	182 (9.7)
	Multiple drugs (N=140)	**2.35 (1.38-4.02)**	25 (17.9)

[a] Adjusted for sex, familial background, socio-economic status, family history of mental disorder, and other problems with family or school. The N behind the response categories refers to the number of records.

Table 4:

Discrete-time hazard models for multivariate associations between substance use and high scores on the “schizotypal signs” subscale. Only significant predictors are shown.

Substance-use variables[a]		**Occurrence of target event**	
		OR (95% CI)	N of target events (%)
Frequency of cannabis use in adolescence:	None (N=1749)	1 (Reference)	144 (8.2)
	Casual (N=320)	**1.80 (1.24-2.59)**	46 (14.4)
	Regular (N=131)	**2.60 (1.59-4.23)**	26 (19.8
Alcohol misuse in adulthood:	No (N=2061)	1 (Reference)	197 (9.6)
	Yes (N=162)	**1.39 (1.02-1.90)**	20 (12.3)

[a] The N behind the response categories refers to the number of records.

Table 5:

Discrete-time hazard models for multivariate associations between substance use and high scores on the “schizophrenia nuclear symptoms” subscale. Only significant predictors are shown.

Substance-use variables[a]		**Occurrence of target event**	
		OR (95% CI)	N of target events (%)
Frequency of alcohol intoxication in adolescence:	No intoxication (N=853)	1 (Reference)	68 (8.0)
	Casual (N=1088)	**1.59 (1.14-2.21)**	128 (11.8)
	Regular (N=153)	1.69 (0.91-3.14)	22 (14.4)
Multiple-drug use in adolescence:	No multiple-drug use (N=1876)	1 (Reference)	182 (9.7)
	Multiple drugs (N=140)	**1.75 (1.01-3.03)**	25 (17.9)

[a] The N behind the response categories refers to the number of records.

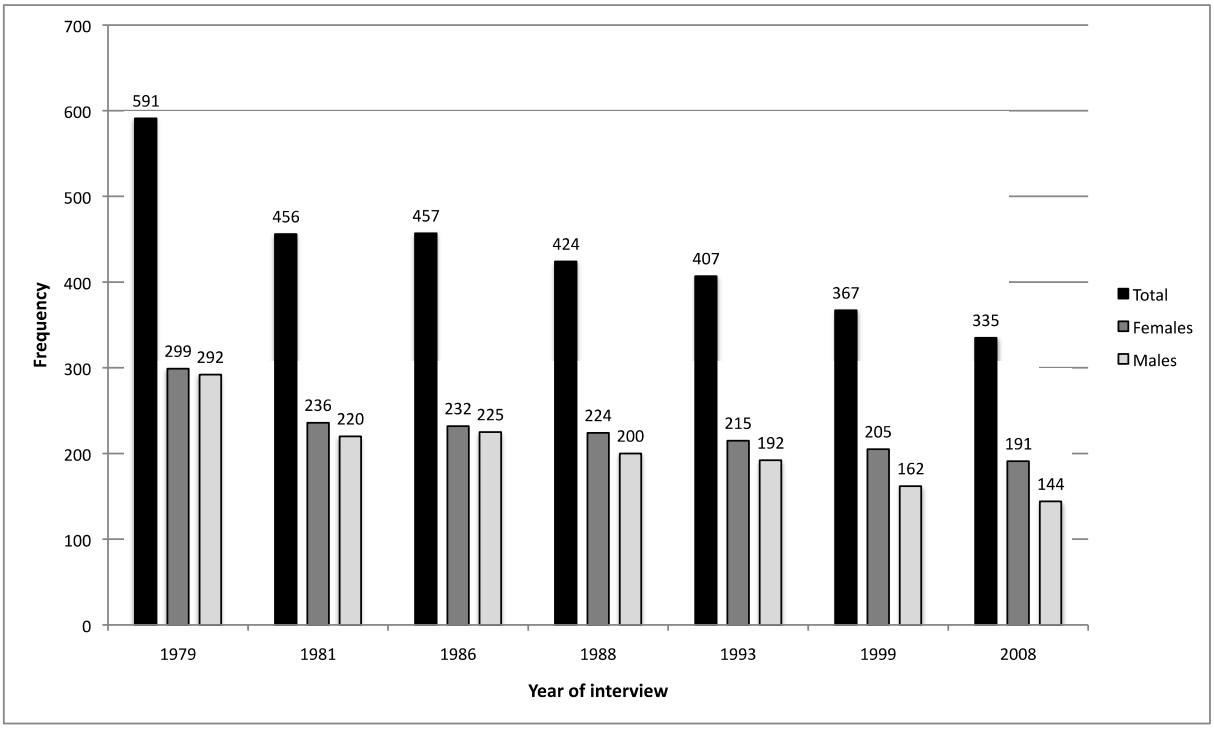

Fig 1:

Numbers and sex of participants over seven assessment waves.

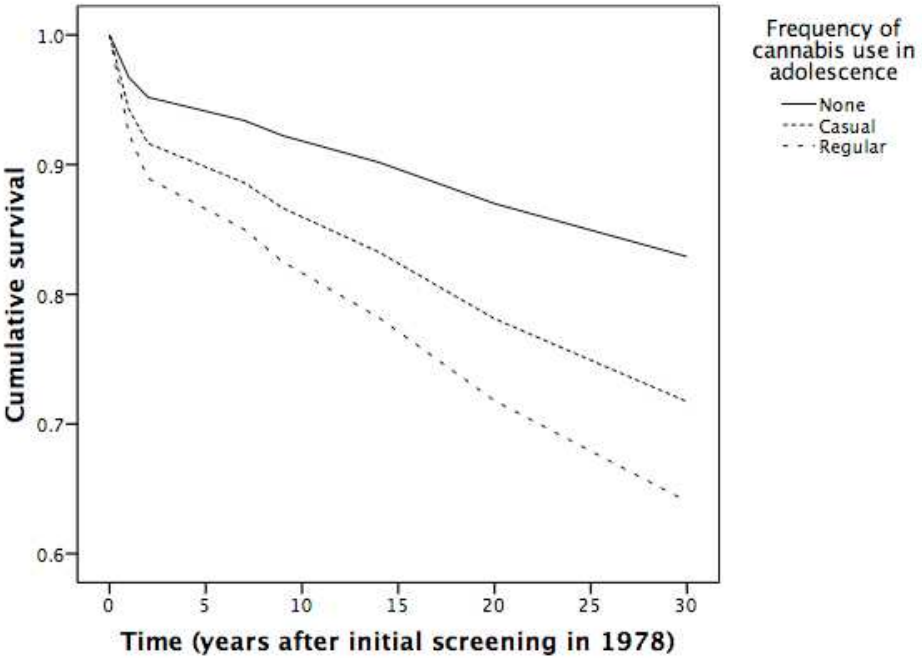

Fig 2:

Survival function for the frequency of cannabis use in adolescence and the occurrence of schizotypal signs.

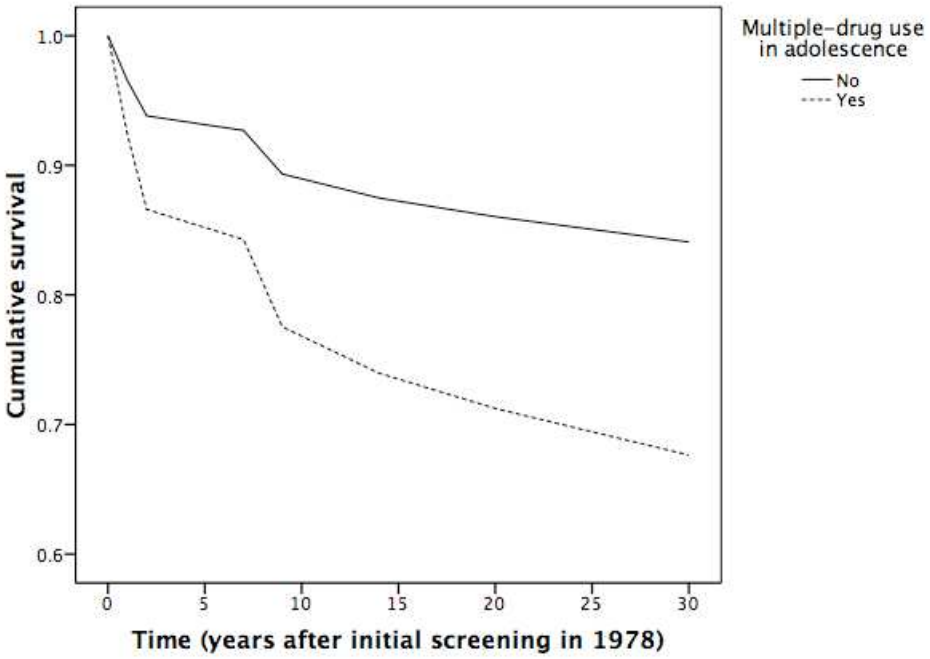

Fig 3:

Survival function for multiple-drug use in adolescence and the occurrence of schizophrenia nuclear symptoms.

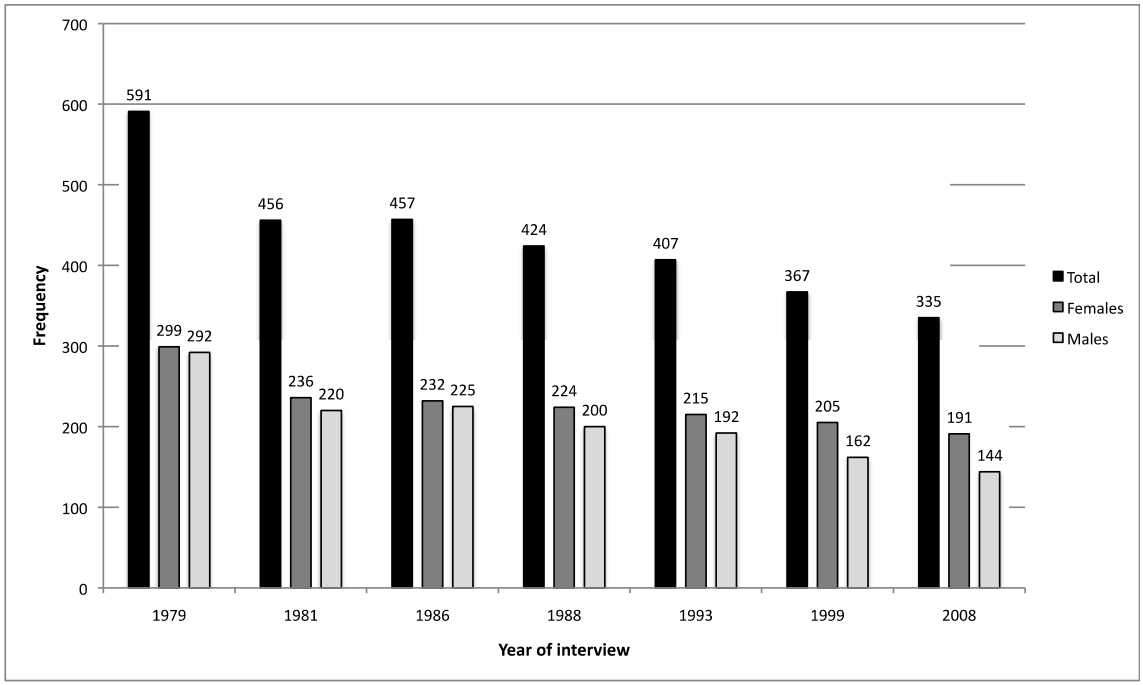

Fig 1:

Numbers and sex of participants over seven assessment waves.

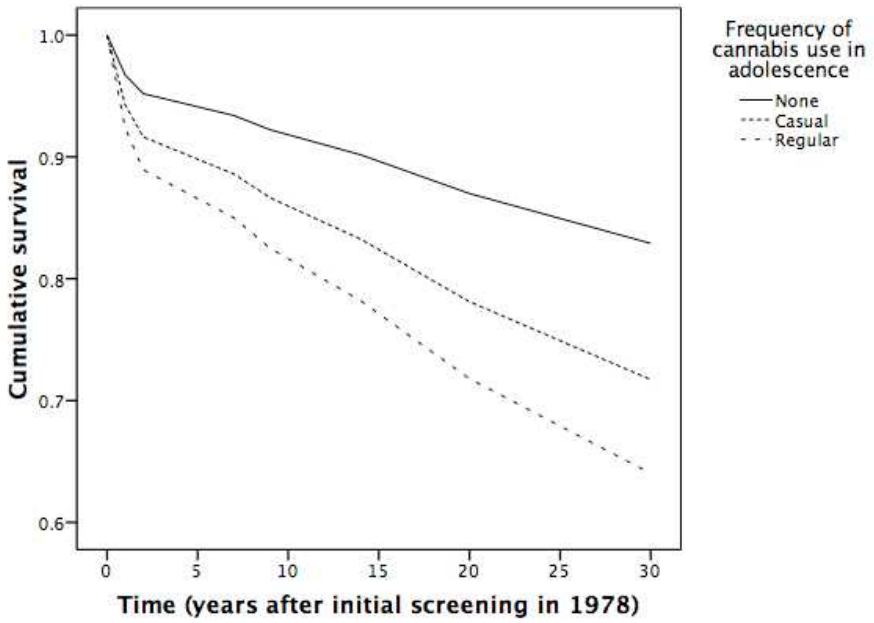

Fig 2:

Survival function for the frequency of cannabis use in adolescence and the occurrence of schizotypal signs.

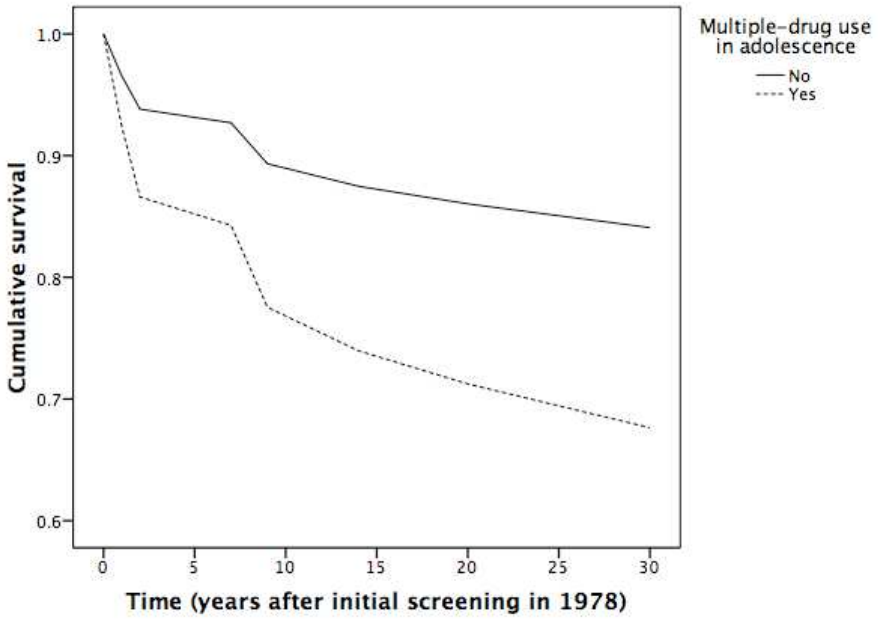

Fig 3:

Survival function for multiple-drug use in adolescence and the occurrence of schizophrenia nuclear symptoms.